AMENDMENTS TO THE SPECIFICATION

Please insert before the BACKGROUND OF THE INVENTION:

INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ELECTRONICALLY

Incorporated by reference in its entirety herein is a computer-readable nucleotide/amino acid sequence listing submitted concurrently herewith and identified as follows: One 12,000 Byte ASCII (Text) file named "230591sequence.TXT," created on July 3, 2007.

Replace paragraph [0003] with:

A cytokine most closely related to IL-2 and IL-15 has been identified and is designated IL-21, and its class I receptor is designated IL-21R. Parrish-Novak et al. suggest that IL-21 plays a role in the proliferation and maturation of natural killer cells from bone marrow, in the proliferation of mature B cells co-stimulated with anti-CD40, and in the proliferation of T cells co-stimulated with anti-CD3 (Parrish-Novak et al., *Nature* 408: 57-63, 2000). Sequencing of the full-length clone, IL-21R, demonstrated that this cDNA contained an open reading frame encoding a 538 amino acid protein having structural motifs common to class I cytokine receptors (Cosman, *supra*; Bazan, *Proc. Natl. Acad. Sci., USA* 87: 6934-6938, 1990). Extracellular motifs include a single cytokine recognition module, two pairs of conserved cysteine residues, and a 'WSXWS' (SEQ ID NO: 5) motif. The intracellular domain contains strong intracellular signaling motifs, including classical box 1 and box 2 motifs (Murkami et al. *Proc. Natl. Acad. Sci., USA* 88: 11349-11353, 1951; Drachman and Kaushansky, *Proc. Natl. Acad. Sci., USA* 94: 2350-2355, 1997; Gurney, et al. *Proc. Natl. Acad. Sci., USA* 92: 5292-5296, 1995), which indicate that the receptor can be a signaling subunit. IL-21R (GenBank Accession numbers AF254067 (human IL-21R) and AF254068 (mouse IL-21R)) was shown to have the highest amino acid sequence similarity to IL-2R and IL-4Rα. Subsequently, Parrish-Novak et al. cloned mouse IL-21R from a mouse splenocyte library, and found that it shares overall structural and functional motifs with human IL-21R (Parrish-Novak et al., *supra*). Further, Parrish-Novak et al. describe the potent effects of IL-21 on all classes of lymphocytes: B, T, and natural killer cells (Parrish-Novak et al., *supra*).

Additionally, Ozaki et al. found IL-21R abundantly expressed in lymphoid tissues, where expression occurs via the T cell antigen receptor, suggesting that the immune system can play a role (*Proc. Natl. Acad. Sci., USA* 97:11439-11444, 2000).

Replace paragraph [0029] with:

A "variant" of the IL-21 polypeptide refers to an amino acid sequence that is altered by one or more amino acids. The variant can have "conservative" changes, wherein a substituted amino acid has similar structural or chemical properties, e.g., replacement of leucine with isoleucine. More rarely, a variant can have "non-conservative" changes, such as, for example, replacement of a glycine with a tryptophan. Minor variations can also include amino acid deletions or insertions, or both. Guidance in determining which amino acid residues can be substituted, inserted, or deleted without abolishing functional, biological or immunological activity can be found using computer programs well known in the art, for example, ~~DNASTAR~~ DNASTAR® software. For purposes of the present invention, the variant preferably has an amino acid sequence that is at least 50% identical to the amino acid sequence of IL-21. More preferably, the variant has an amino acid sequence that is at least 85% identical to the amino acid sequence of IL-21. Most preferably, the variant has an amino acid sequence that is greater than 95% identical to the amino acid sequence of IL-21.

Replace paragraphs [0047] and [0048] with:

"Control elements" or "regulatory sequences" are those non-translated regions of the vector, e.g., enhancers, promoters, 5' and 3' untranslated regions, which interact with host cellular proteins to carry out transcription and translation. Such elements can vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription and translation elements, including constitutive and inducible promoters, can be used. For example, when cloning in bacterial systems, inducible promoters, such as the hybrid lacZ promoter of the ~~BLUESCRIPT~~ BLUESCRIPT® phagemid (Stratagene; La Jolla, CA) or PSPORT1 plasmid (Life Technologies; Rockville, MD), and the like, can be used. The baculovirus polyhedrin promoter can be used in insect cells. Promoters or enhancers derived from the genomes of plant cells (e.g., heat shock, RUBISCO; and storage protein genes), or from plant viruses (e.g., viral promoters or leader sequences), can be cloned into the vector. In mammalian cell systems, promoters from

mammalian genes or from mammalian viruses are preferred. If it is necessary to generate a cell line that contains multiple copies of the sequence encoding IL-21, vectors based on SV40 or EBV can be used with an appropriate selectable marker.

In bacterial systems, a number of expression vectors can be selected, depending upon the use intended for the expressed IL-21 product. For example, when large quantities of expressed protein are needed for the induction of antibodies, vectors which direct high-level expression of fusion proteins that are readily purified can be used. Such vectors include, but are not limited to, the multifunctional *E. coli* cloning and expression vectors, such as ~~BLUESCRIPT~~ BLUESCRIPT® (Stratagene; La Jolla, CA), in which the sequence encoding the IL-21 polypeptide can be ligated into the vector in-frame with sequences for the amino-terminal Met and the subsequent 7 residues of ß-galactosidase, so that a hybrid protein is produced; pIN vectors (see, Van Heeke and Schuster, 1989, *J. Biol. Chem.*, 264:5503-5509); and the like. pGEX vectors (Promega; Madison, WI) also can be used to express foreign polypeptides, as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can be easily purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. Proteins made in such systems can be designed to include heparin, thrombin, or factor XA protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety at will.

Replace paragraph [0090] with:

The statistical analyses to compare tumor growth rate and mouse survival rate between treatment and control groups were determined by ANOVA— Repeated Measures test using the ~~StatView~~ StatView™ program (Abacus Concepts, Berkeley, CA). The statistical analyses to compare tumor sizes and cell numbers between treatment and control groups were determined by the nonparametric Kruskal-Wallis test using the StatView program.

Replace paragraph [0093] with:

Human PBMC and murine spleen cells (C57BL/6) were activated by 5 ng/ml of PMA and 250 μg/ml Ionomycin for 24 hr. Total RNA was extracted and isolated by ~~TRIZOL~~ TRIZOL® method (Life Technologies/Invitrogen; Carlsbad, CA). RT-PCR was performed to amplify the first strand of cDNA by random primers according to manufacturer's

instruction (ThermoScript RT-PCR System; Life Technologies/ Invitrogen). The full-length cDNA fragment (including the original signal peptide) was PCR amplified using a pair of specific primers for either human or murine IL-21.

Replace paragraph [0099] with:

Freshly isolated murine splenocytes from C57BL/6 mice were activated with 5 ng/ml PMA and 250 μg/ml ionomycin for 24 hr. Total RNA was extracted using ~~TRIZOL~~ TRIZOL® (Invitrogen/Life Technologies). RT-PCR was performed to amplify the first strand of cDNA by random primers using ~~ThermoScript~~ ThermoScript™ RT-PCR System (Invitrogen/Life Technologies). The full-length mIL-21 cDNA fragment was PCR amplified using PCR SuperMix High Fidelity (Invitrogen/Life Technologies) and the primers of SEQ ID NOS: 3 and 4. The full-length murine IL-21 cDNA fragment was digested and cloned into the pORF-mcs vector under the control of an elongation factor-1 α/human T-cell leukemia virus (EF-lo/HTLV) hybrid promoter (InvivoGen, San Diego, CA), and was designated as pORF/mIL-21. The correct sequence of murine IL-21 was confirmed by sequence analysis. To exclude endotoxin contamination, a large preparation of pORF/mIL-21 and the control pORF plasmid DNA was purified using the ~~EndoFree~~ EndoFree™ Plasmid Mega Kit (QIAGEN, Valencia, CA).

Replace paragraph [00117] with:

The growth inhibition of tumor cells *in vitro* was determined by a 72-h MTS assay using the CellTiter 96® AQueous ~~CellTiter 96Aqueous~~ One Solution Assay kit according to manufacturer's instruction (Promega, Madison, WI). Briefly, $1x10^5$ murine tumor cells, including MCA205, B16, 24JK and MC38, were plated in 24 well plates in 1 mL of RPMI complete medium in combination with various amounts of recombinant mIL-21 protein. After 3 days, 100 μL of culture medium from each well were collected and incubated with 20 μL of MTS reagent at 37°C for 2 hr. Absorbance at 490 nm was then measured to determine the relative cell growth between groups.